REMARKS

Claims 1-24 are pending in the application. Claims 8-14 stand withdrawn pursuant to a Restriction Requirement made Final in the Office Action mailed July 18, 2003.

Claim 1 has been amended to clarify the language. The claim now provides a method for increasing active IGF-I levels in a mammal. Support for this language can be found in the specification at, for example, page 4, lines 24-35, page 12, lines 4- 12 and page 13, lines 24-26, page 22, lines 31-32 and Example 3.

Claim 2 has been amended to clarify the language and to be consistent with the language of newly amended Claim 1. Support for this amendment can be found in the specification at, for example, page 7, lines 25 – 28 and page 41, lines 25 - 27.

Claim 3 has been amended to recite a method for treating reduced renal function in a mammal. Support for this language can be found in the specification at, for example, page 5, line 16 - page 6, line 8.

Claim 4 has been amended to be consistent with the language of newly amended Claim 3 upon which it depends.

Claim 5 has been amended to clarify the language. Support for this amendment can be found in the specification at, for example, page 26, lines 1 -13.

New Claims 17 - 24 have been added. Support for Claims 17 - 21 can be found in the specification, for example, at page 5, line 16 - page 6, line 8 and in original claims 3-7.

Support for claims 22-24 can be found in the specification at, for example, page 12, lines 16-18 and original claims 1 and 6-7.

No new matter is added by way of the amendments.

Withdrawn Rejection

Applicants gratefully acknowledge the withdrawal of the rejection to Claims 1-7 under 35 U.S.C. §112, second paragraph.

Rejection of Claims 1-7 under 35 U.S.C. §112, first paragraph

Claims 1-7 and 15-16 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The claims contain subject matter which allegedly was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner has indicated that the specification is enabling for a method of treating reduced renal function, a method of enhancing renal function and a method of treating type II diabetes in a mammal comprising administering to the mammal an effective amount of an IGF-I variant of the invention.

Applicants have amended Claim 3 to recite a method of treating reduced renal function in a mammal. Applicants believe that this amendment overcomes the rejection of Claim 3 and Claims 4-5 and 15-16 that depend on Claim 3. Allowance of Claims 3 - 5 and 15-16 is therefore respectfully requested.

Applicants have added new Claims 17- 21 which recite a method of enhancing renal function in a mammal. Applicants believe that these new claims are patentable in view of the specification and Examiner's remarks.

Applicants have added new Claims 22 - 24 which recite a method of treating Type II diabetes. Applicants believe that these new claims are patentable in view of the specification and Examiner's remarks.

Claim 1 (as amended) now recites methods for increasing active IGF-I levels in a mammal by administering to a mammal an effective amount of an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions

3 and 49 of the native sequence human IGF-I are replaced with an alanine, a glycine or a serine residue.

The Patent Office states that the term "disorder characterized by dysregulation of the GH/IGF axis" in the claims is interpreted to be broad in that it encompasses any and all diseases or disorders involved in the regulation of anabolic and metabolic homeostasis. The specification allegedly does not teach treating any disorder characterized by dysregulation of the GH/IGF axis in a mammal by administration of any IGF-I variant.

Without acquiescing to the Examiner's arguments, Applicants have removed the language objected to by the Examiner. The amendment of Claim 1 serves to clarify the claim language but does not narrow its scope. Applicants believe that the amendments to Claim 1 overcome the rejection by the Examiner.

Applicants maintain that there is sufficient disclosure in the specification to be enabling for amended Claims 1 and 6-7.

The amount of disclosure required to be supplied by an enabling specification has been discussed and defined in court decisions. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also* Amgen Inc. v. Chugai Pharms. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991). "That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is undue" In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991). "Enablement is not precluded by the necessity for some experimentation ... [the] experimentation needed to practice the invention must not be undue experimentation." Enzo Biochem, Inc. v. Calgene, Inc. 188 F.3d 1362, 1371 (Fed. Cir. 1999).

The initial burden is on the Patent Office to provide a reasonable explanation of why the specification does not enable the scope of the protection claimed. Only after the PTO provides evidence showing that one of ordinary skill in the art would

reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. In re Brana, 51 F3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995)

The Patent Office has indicated that the language "disorder characterized by dysregulation of the GH/IGF axis" is interpreted to be broad. The Office Action further states that one skilled in the art would not be able to predict from the instant specification that an IGF-I variant recited in the claims would be able to treat all possible diseases, such as Down's syndrome and congestive heart failure because these disease have different pathophysiologies.

Applicants have clarified that the claimed invention as set forth in Claim 1 is directed to a method for increasing active IGF-I levels in a mammal through administration of IGF-I variants.

The Examiner has stated that undue experimentation would be required by the skilled artisan to identify individuals with a renal disorder or a disorder characterized by dysregulation of the GH/IGF axis, such as by measuring IGFBP-1 and IGFBP-3 levels.

Applicants disagree. Undue experimentation would not be required to identify individuals with reduced IGF-I levels. Determination of levels of active IGF-I, IGFBP-1 and IGFBP-3 can be done through standard clinical means, for example ELISA for levels of molecules, clinical chemistry RIA or bioassay. See, for example page 22, lines 11 – 30, which describe methods for measuring the level of active IGF-I levels. See also Example 3, page 41-42 which describes measurements of IGF-I in rats and Example 4, pages 42-43, International Patent Application No. WO98/45427, and U.S. Patent No. 5,565,428, both published before the effective filing date, which describe methods of measuring IGF-I, IGFBP1 and IGFBP3. Thus, one skilled in the art based on the disclosure in the specification and the cited patent disclosures would know how to measure levels of IGF-I, IGFBP-1 and IGFBP-3.

Further, the Office Action states that Claims 1-7 and 15-16 do not specify what specific effect the IGF-I variant has. A large quantity of experimentation would be

required by one of skill in the art allegedly to determine the effect/endpoint indicating that a particular disorder has been treated.

Applicants describe precisely the IGF-I variants of the claimed invention and show that the variants bind IGFBP-1 very weakly while retaining high affinity binding of IGFBP-3. See for example, Example 1, page 27-38 and Tables I and II. The binding affinities of the double mutants are shown in Example 2, Table III, pages 38 - 42. Example 2 shows that the variants have significantly reduced binding affinities for IGFBP-1, but retain the same binding affinity to IGFBP-3 as the wild-type IGF-1. Example 2 further describes the KIRA assay of IGF-I type receptor activation and shows that the variants maintain the ability to activate the IGF-I receptor. Therefore, the variants are fully biologically active. Example 2 also shows that the variant F49A and the E3A.F49A double mutant accumulate at higher levels in the kidneys of rats compared to wild-type IGF-I. The specification states that this would be beneficial for renal failure.

Claims 3, 17, and 22 recite methods of treating reduced renal function, enhancing renal function, and treating type II diabetes, respectively. The specification clearly teaches that the IGF-1 variants claimed would be effective to treat all of these conditions. Further, applicants have claimed in Claim 1 a method for increasing active IGF-I levels in a mammal. Clearly, for this claim, an effective amount of the variant would be that amount needed to raise the level of active IGF-I in the mammal to normal levels.

Use of wild-type IGF-I to treat mammals suffering from kidney disorders, renal dysplasias, and /or renal hypoplasias is described in U.S. Patent No. 5,985,830. On page 12 of the Office Action, the Examiner has stated that "Applicant has only provided evidence that IGF-I is used to treat renal dysplasias, renal hypoplasias and chronic renal failure, AIDS associated cachexia and type II diabetes (U.S. Patent 5,565,428 and 5,741,776)". Applicants specifically and categorically disagree with the Examiner's statement regarding these patents and believe that the Examiner has mischaracterized these patents. U.S. Patent No. 5,565,428 is directed to a method for treating chronic

renal failure in a mammal. U.S. Patent No. 5,741,776 is directed to a method for administering insulin-like growth factor I (IGF-I) to a mammal so as to sustain its biological response in the treatment of **any** chronic disorder in the mammal. There is a wide range of chronic disorders set forth in that patent. The issuance of those patents presumptively shows that the specifications and examples in those patents support the broader claims that issued.

Applicants rely on U.S. Patent No. 5,565,428 and 5,741,776 as teaching various methods of administration and dosages of wild-type IGF-I to treat human patients for a broad range of diseases. Accordingly, an IGF-I variant of the instant invention could be administered by these methods.

For the above reasons, Applicants maintain that their specification is fully enabling for the claimed invention. Withdrawal of this rejection is respectfully requested.

The Rejections to Claims 5 under 35 U.S.C. §112, first paragraph

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph as containing subject matter which is not described in the specification so as to convey that the inventor had possession of the claimed invention. Specifically the specification allegedly does not describe an "antibody molecule that promotes readsorption or retention of electrolytes".

Applicants have amended Claim 5 to clarify the claim language.

Applicants direct the Examiner to page 26, lines 1-13 which recite "renally active molecules that promote readsorption and retention of electrolytes". The specification then lists a number of examples, one of which is endothelin antagonists such as antibodies. Endothelin antibodies were known in the art at the filing date of the application. Applicants enclose the abstracts from two papers published prior to the filing date which refer to endothelin antibodies (Urakami et al., *J. Am Coll. Surg.* 1997 vol. 185(4) 358-64 and Miyamori et al., *Clin Exp. Pharmacol. Physiol.* 1990 vol. 17(10)

691-6). Accordingly, Applicants did have possession of the claimed invention at the time of filing.

Withdrawal of this rejection is respectfully requested.

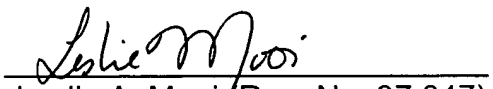
CONCLUSION

For the reasons set forth above, Applicants believe that all claims are in condition for allowance. Should the Examiner believe that a telephone interview would expedite the prosecution of this application, Applicants invite the Examiner to call the undersigned attorney at the telephone number indicated below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** referring to Attorney's Docket No. **39766-0131 R1-1D1**.

Respectfully submitted,

Dated: January 24, 2005

By: 
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